REMARKS

The undersigned confirms having discussed the above application with the Examiner in the telephone conversation on October 19, 2006. At that time, the new matter rejection as to the range "80mg/mL to about 400mg/mL" was discussed. The undersigned pointed out that disclosure of "about 80mg/mL" as a lower limit for the range would clearly inform the skilled person that "80mg/mL" was contemplated. In addition, undersigned explained that case law supported Applicants' ability to combine an upper and lower limit for a range from different places in the patent specification. Notwithstanding this, following a suggestion of the Examiner, independent claims 42 and 47 are amended herein to refer to the range from "about 50mg/mL to about 400mg/mL." Applicants explained that such claimed range of antibody concentration was not disclosed or suggested by the previously relied-upon art, namely US Patent No. 5,770,195 ("the '195 patent"), which referred to a formulation with "about 1 mg/ml to 10mg/ml" of the HER2 antibody. (Moreover, the '195 patent did not disclose subcutaneous administration of the antibody, as in the present claims.)

Amendments

Claims 42 and 47 are amended herein to refer an amount of the antibody from "about 50mg/mL to about 400mg/mL," as supported on page 22, line 28. In addition, those claims now refer to "an antibody which binds to an extracellular domain of HER2 receptor," with support for that recitation being found on at least page 25, line 15.

New claims 53-59 are added, with support therefor being found at least as follows:

claim 53 - page 2, line 16, and page 22, line 28 for "from 50mg/mL"

claim 54 - page 22, lines 28-29 (note MPEP 2163.05 (III) supports Applicants' ability to combine upper and lower range limits inherently supported by the disclosure)

claim 55 - page 22, line 29

claim 56 - page 22, line 29, where disclosure of about 80mg/mL at line 22 provides inherent support for 80mg/mL as a range limitation (see MPEP 2163.05 (III))

claim 57 - page 10, line 24; page 24, line 11; page 25, lines 27-28

claim 58 - claim 42; page 10, line 24; page 24, line 11; page 25, lines 27-28 (for a recombinant humanized anti-HER2 (rhuMAb HER2) antibody); and page 2, line 16 for "from 50mg/mL"

claim 59 - claim 42; page 10, line 24; page 24, line 11; page 25, lines 27-28 (for a recombinant humanized anti-HER2 (rhuMAb HER2) antibody); and page 22, line 29 for "about 80mg/mL to about 300mg/mL."

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

Section 112, first paragraph - new matter

Claims 42, 44, 46-47 and 51-52 are rejected under 35 USC Section 112, first paragraph as allegedly containing new matter with respect to the recitation of "80mg/mL to about 400mg/mL."

Applicants traverse the first element of the rejection, on the basis that the disclosure of the lower limit of the range of about 80mg/mL (see, for example, page 22, line 29) would clearly inform the skilled person reading the disclosure that such could be 80mg/mL. As explained in MPEP 2163.05 (III), with respect to changing numerical range limitations, the analysis must take into account which ranges *one skilled in the art would consider inherently supported by the discussion in the original disclosure*. Here, the skilled person would most certainly agree that "80mg/mL" as a lower limit of the range was inherently supported by the disclosure of "about 80mg/mL."

With respect to the second element of the rejection related to combining "80mg/mL" with "400mg/mL," Applicants submit that *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) is supportive of Applicants' ability to combine numerical range limitations from different parts of the specification. As explained in MPEP 2163.05 (III), in *Wertheim*, "between 35% and 60%" was supported by a range of "24%-60%" and specific examples of "36%" and "50%."

Notwithstanding the above, following a suggestion by the Examiner in the above-discussed telephonic interview, Applicants have amended claims 42 and 47 herein to recite "from about 50mg/mL to about 400mg/mL" as supported on page 22, line 28, for example.

Reconsideration and withdrawal of the rejection is respectfully requested.

Section 112, first paragraph - enablement

Claims 42, 44, 46-47 and 51-52 are rejected under 35 USC Section 112, first paragraph for allegedly lacking enablement. The Examiner is of the view that

the specification, while enabling cancer therapy with a recombinant humanized HER2 antibody, lacks enablement of such therapy with any and all anti-HER2 antibodies.

Applicants submit that the claims are enabled.

First, Applicants address the Examiner's apparent concern that the claims encompass an antibody which binds to an intracellular portion of the HER2 receptor, or an antibody that binds to another intracellular antigen. In order to obviate this basis of the rejection, claims 42 and 47 are amended herein to refer to "an antibody which binds to an *extracellular domain* of HER2 receptor."

Second, Applicants will address the Examiner's reliance on Stancovski *et al. PNAS (USA)* (1991), Lewis *et al. Cancer Research* (1996), and Strobel *et al. Gynecol. Oncol.* (1999), as purportedly teaching that one skilled in the art cannot predict whether an anti-HER2 receptor antibody that binds an extracellular domain of the HER2 receptor will function to inhibit the growth of tumor cells *in vivo*, even if the antibody is known to inhibit an activity of the receptor.

Applicants traverse this second basis of the rejection. The present application was filed at a time when the art, coupled with the patent disclosure, provided information on how to make and screen for HER2 antibodies which inhibited growth of HER2 overexpressing tumor cells *in vivo*. For example, the '195 patent filed in 1988 (well before the 1996 filing date of the present application), disclosed how to make (several) HER2 antibodies that inhibited such tumor growth *in vitro* (columns 17-18) and *in vivo* (column 19). Aside from the 4D5 antibody (humanized form, HERCEPTIN®, exemplified in the present application), the 3E8 antibody was also effective in inhibiting tumor growth *in vivo* (Table 2 in column 19). Thus, Applicants submit that the specification at the time of filing enabled a genus of HER2 antibodies with the ability to inhibit growth of HER2 overexpressing tumor cells.

The cited references do not detract from this knowledge in the art at the time of filing. Stancovski generated a panel of antibodies to the HER2 extracellular domain, including N29 and N12, which inhibited tumor growth *in vivo*. Antibodies N10 and N24 were less efficient at tumor inhibition. MAb N28 stimulated tumor growth. So, in addition to the 4D5 and 3E8 antibodies in

the '195 patent, by the time of filing, Stancovski had disclosed additional antibodies (N29 and N12) which inhibited tumor growth *in vivo*. (The skilled person would *know* not to use N28 in the presently claimed method.)

So, the story that emerges from reviewing the '195 patent and Stancovski is that a *genus* of antibodies, including 4D5, 3E8, N29, and N12 with the ability to inhibit tumor growth *in vivo* had been disclosed by the time the above application was filed. While one antibody, namely N28, had been reported to stimulate tumor growth, the skilled person would not have had to exercise extraordinary skill to know not to use such an antibody in the presently claimed method, particularly since the claims herein require that the method involve administration of a "therapeutically effective" amount of the antibody. In other words, since the claims herein recite "administering to the human subcutaneously a *therapeutically effective amount* of a formulation comprising *an antibody which binds to an extracellular domain of HER2 receptor*," they effectively exclude therapeutically ineffective antibodies (such as the N28 antibody), which the skilled person could have readily identified and eliminated at the time of filing.

As to the other reference relied upon in the Section 112 rejection, Lewis *et al. Cancer Research* (1996), Applicants submit that this reference *actually supports* the enablement of the presently claimed method. The Examiner appears to urge that Lewis *et al.* reports the phenomenon of an antibody that accelerates tumor growth. Applicants disagree. Rather, Lewis *et al.* reports that HRG stimulation of tumor cell growth is inhibited by anti-HER2 MAbs 2C4 and 7F3. Thus the genus of HER2 antibodies that can be used in the presently claimed method increases: 4D5, 3E8, N29, N12, 2C4, 7F3. Indeed, a humanized form of the 2C4 antibody has been shown to be effective to shrink tumors in patients with several different types of cancers. See http://www.newswise.com/articles/view/?id=2C4ASCO.CED (Attachment A hereto)

Thus, Applicants submit that the evidence supports the enablement of the claims for therapy with a *genus* of different HER2 antibodies.

Turning now to Strobel, Applicants submit that this is less relevant that the other references (Stancovski and Lewis; which are supportive of the enablement of a genus of HER2 antibodies as noted above), since it relates to antibodies to an unrelated antigen, β1-integrin. Strobel would not disprove that a genus of HER2 antibodies with *in vivo* growth inhibitory function useful in the

presently claimed methods were described by the time the above application was filed.

In view of the above, reconsideration and withdrawal of the Section 112 rejection is respectfully requested.

Respectfully submitted,
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Date October 20, 2006

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Attachment A

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Experimental Drug Shrinks Tumors

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Medical News

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Description
An early clinical trial at the Cedars-Sinai Medical Center has shown that an experimental drug called 2C4 (trade name is Omnitarg) was effective to shrink tumors in patients with several different types of cancer.

As more is learned about how cancer develops, scientists have begun designing new drugs that directly target cancer cells, leaving healthy ones intact. Having fewer side effects, some of these drugs work by blocking growth signaling processes within cancer cells, while others enlist the body's immune system to recognize and mount an attack against the cancer cell. But regardless of how they work, most of these drugs are designed to treat a specific cancer and cannot be used to treat other tumor types.

Now, an early clinical trial at the Cedars-Sinai Medical Center has shown that an experimental drug called 2C4 (trade name is Omnitarg) was effective to shrink tumors in patients with several different types of cancer. The findings, presented at the 39th annual meeting of the American Society of Clinical Oncology in Chicago, may lead to a new way to treat various types of cancer.

"What's interesting is that this drug effectively shrank tumors in several completely different types of cancer in early stage clinical trials," said David Agus, M.D., Research Director at the Cedars-Sinai Prostate Cancer Center and first author of the study. "This tells us that the drug targets a growth signaling pathway in cancer cells that is common in many solid tumors."

The drug, called 2C4 and developed by Genentech, Inc., is a monoclonal antibody, or protein that enlists the body's immune system to attack foreign invaders, such as viruses or bacteria. It works by targeting HER-2/neu, a member of the HER kinase family of proteins. The protein sits on the surface of cancer cells and receives signals from growth factor molecules within the HER family, which in, turn stimulate tumors to grow.

But earlier research in Dr. Agus' laboratory indicated that 2C4 was not limited to targeting HER-2/neu alone and blocked signaling activity among the entire HER network of proteins in both breast and prostate cancer tumors grown in mice. These findings led the investigators to begin the first clinical trial to test the safety and effectiveness of the drug in patients with other types of solid-tumor cancers.

In the study, 21 patients with advanced cancers including breast, prostate, lung, ovarian, colon, pancreas and sarcoma received 2C4 by infusion every three weeks at a dose level ranging between 0.5 and 15 milligrams per kilogram of body weight. Among these patients, 19 completed at least two cycles or six weeks of treatment with 2C4, while two died at the outset of treatment due to complications of their disease. The investigators found that eight or 42 percent of the 19 patients treated with 2C4, responded to treatment either because their tumors shrank over 50 percent, or because their tumors stopped growing for a given time period before their disease progressed. (Cedars-Sinai IRB No. 3691)

Of the 19 patients who received 2C4, three achieved partial remission as measured by shrinkage of their tumors by over 50 percent. These included one patient with ovarian cancer, who received 5 mg/kg of 2C4; one with prostate cancer, who received 15 mg/kg of 2C4; and one patient with a pancreatic neuroendocrine cancer who received 15 mg/kg of 2C4. Two of these patients (ovarian and pancreatic cancer) remain in remission and have been receiving 2C4 for over a year since beginning therapy.

"To see results that show activity in a Phase I safety trial is remarkable, especially since these patients were in the advanced stages of their disease and had no other treatment options available to them," said Dr. Agus. "This is especially exciting as there was little drug related toxicity or side effects associated with this treatment."

In addition, the investigators report that five additional patients' disease stabilized for at least three months after just two treatment cycles with 2C4. These patients included three with cancers of the prostate, one with non-small cell lung cancer and one with ovarian cancer.

"Targeting a pathway, rather than a tumor type, is an exciting new area in the treatment of cancer, and 2C4 is one of several experimental drugs that show how this treatment strategy can benefit patients," commented Dr. Agus.

A Phase II clinical trial with 2C4 started in May, 2003 at Cedars-Sinai Medical Center to evaluate the effectiveness of the drug in patients with advanced cancers of the prostate, (Cedars-Sinai IRB No. 4100-01) and is scheduled to be open for ovarian cancer patients in June.

Cedars-Sinai Medical Center is one of the largest non-profit academic medical centers in the Western United States. For the fifth straight two-year period, Cedars-Sinai has been named Southern California's gold standard in health care in an independent survey. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthroughs in biomedical research and superlative medical education. Named one of the 100 "Most Wired" hospitals in health care in 2001, the Medical Center ranks among the top 10 non-university hospitals in the nation for its research activities.
